Modulation of Immunity by Ultraviolet Radiation: Key Effects on Antigen Presentation

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In addition to being the major cause of non-melanoma skin cancer, the ultraviolet radiation (UVR) present in sunlight is a potent immunosuppressive agent. Indeed, studies with mice and humans have indicated that the immune suppression induced by UVR is a risk factor for skin cancer development. These observations gave rise to the discipline of photoimmunology, which studies the interaction of electromagnetic radiation, primarily UVB (280–320 nm) light, with the immune system. The focus of this paper will be to review recent studies designed to unravel the mechanisms through which UVR suppresses immune reactivity. Particular emphasis is placed on the effects of UVR on antigen presentation.
Key words: cytokines/immunosuppression. J Invest Dermatol 105:30S–36S, 1995

The ultraviolet radiation (UVR) present in sunlight has the potential to affect adversely human health and well being. In addition to being the major cause of non-melanoma skin cancer, UVR also induces sunburn and erythema, promotes premature aging of the skin, causes ocular damage, including keratitis and cataracts, damages immune competent cells within the skin, and induces systemic immune suppression. Although scientists and physicians have recognized for almost 100 years that UVR induces skin cancer, the realization that UVR alters the immune response became apparent during the work of Kripke, who was studying the biology of UV-induced skin cancer in mice. Unlike most murine tumors, the UV-induced skin tumors failed to grow progressively when transplanted into normal syngeneic recipient mice. These "regressor" tumors would only grow when transplanted into an immunocompromised host, suggesting that the UV-induced tumors were highly antigenic and were rejected by the immune response of the normal mice. How then did these highly antigenic tumors escape the immune response in the UV-irradiated autochthonous host? Subsequent studies by Kripke and colleagues and Daynes and coworkers (reviewed in [1,2]) demonstrated that exposing mice to subcarcinogenic doses of UV radiation suppresses cell mediated immunity by inducing the production of antigen-specific suppressor T cells that transferred the suppressive state to normal recipient mice. Moreover, these suppressor T cells were shown to be involved in the development of the primary tumor in the UV-irradiated animals. Thus, these studies demonstrated that in addition to being carcinogenic, UVR is also immunosuppressive, and the ability of UVR to suppress immunity is associated with its ability to induce skin cancer in mice. It is important to note that more recent studies with biopsy-proved skin cancer patients have also suggested the immune suppression induced by UVR is a risk factor for skin cancer development in humans [3].

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Abbreviations: APC, antigen-presenting cells; CHS, contact hypersensitivity; MIP, macrophage inflammatory protein; Th1, T helper 1 cells; Th2, T helper 2 cells.

The association between skin cancer induction and immune suppression has been a driving force behind the efforts of many to understand the mechanisms involved in the induction of immune suppression by UVR. The focus of this report will be to review recent efforts to unravel the pathways by which UVR depresses the immune response.

MODULATION OF ANTIGEN-PRESENTING CELL (APC) FUNCTION BY UVR IS A KEY TO THE INDUCTION OF NON-RESPONSIVENESS

Effects of UVR on APC Populations in the Skin: Direct Effects of UV Exposure The target of UVR is the skin, and one of the first hints that UV exposure was altering APC function *in vivo* came from the work of Toews *et al* [4], who examined the effect of UV radiation on the epidermal APC, the Langerhans cell (LC). In normal skin, LC form a dendritic network of cells through the epidermis. Presumably one function of these cells is to trap antigen, migrate to the regional lymph nodes, and present the antigen to T cells [5]. Toews *et al* demonstrated that UVR alters the morphology of the epidermal LC, the dendritic processes were destroyed, and fewer cells within the irradiated epidermis stained for LC markers (major histocompatibility complex (MHC) class II antigen and ATPase). In contrast to what happened when a contact allergen was applied to normal skin, application of contact allergens to the UV-irradiated, LC-depleted skin resulted in no induction of contact hypersensitivity. This unresponsiveness did not simply reflect a null event, because the UV-irradiated mice did not respond to a second application of the same hapten, suggesting active immune suppression. Furthermore, antigen-specific suppressor T cells were found in the spleens of the UV-irradiated animals [6]. Data from these experiments suggested that UVR altered the function of LC so that a tolerance-inducing signal rather than an activation signal was sent to the immune system.

Additional observations supported the hypothesis that the UV-induced alteration of LC function activated the suppressive pathway. Cruz and colleagues obtained a relatively pure population of LC by sorting out the I-A^+ epidermal cells [7]. These cells were exposed to UVR and conjugated with hapten *in vitro*. Injecting the UV-irradiated LC into mice prevented the subsequent induction of

0022-202X/95/$09.50 • SSDI0022-202X(95)00155-E

contact hypersensitivity (CHS) when the animals were sensitized with hapten. Furthermore, it was discovered that the UV-irradiated cells transmitted a tolerance-inducing signal to the immune response because the animals did not respond to a second application of the same hapten.

Subsequent data reported by Simon and colleagues [8,9] further supported the hypothesis that UVR alters LC APC function and promotes the induction of T-cell tolerance. In these experiments the ability of UV-irradiated LC to present antigen to two different types of T-cell clones was measured. Two subsets of helper T cells have recently been described in mice [10] and humans [11]. These cells are distinguished primarily on the cytokines they produce and the type of immune responses they participate in. Upon activation, T helper 1 cells (Th1) secrete interleukin (IL)-2, IL-12, and interferon gamma (IFN-γ); help cell-mediated immune reactions (DTH, CHS, CTL, and NK cell activation); and generally help B cells produce complement fixing antibodies (IgG2a and IgG3). T helper 2 (Th2) cells, on the other hand, secrete IL-4, 5, 6, and 10, favor the production of non-complement fixing antibodies (IgG1), and are involved with reactions associated with allergy (IgE release, activation of mast cells and eosinophils). In addition, the cytokines produced by each Th subset can regulate the activity of the other. For example, the IL-12 and IFN-γ produced by Th1 cells can down-regulate the proliferation and differentiation of Th2 cells [12], and the IL-10 produced by Th2 cells can inhibit IFN-γ production by Th1 cells [10]. Although normal LC present antigen to both Th1 and Th2 cells, Simon *et al* discovered that UV-irradiated LC were unable to present antigen to Th1 cells but did retain their capacity to present antigen to Th2 cells [8]. In addition, it was reported that when UV-irradiated LC were used as APC, not only were the Th1 cells non-responsive, they were tolerized. This tolerant state was associated with functional inactivation of the Th1 cells rather than deletion, hence clonal anergy. Thus, these studies support the hypothesis that UVR triggers immune unresponsiveness by altering APC function and point to the epidermal LC as a primary target of UVR in the skin.

It is also clear, however, that modulation of LC function is not the only mechanism by which UVR alters epidermal APC function. As in mice, exposing human skin to UVR depletes epidermal LC. However, in human skin a population of inflammatory cells migrates into the epidermis after UV exposure [13,14]. These $CD1a^-DR^+$ macrophages have been shown to preferentially activate a population of suppressor-inducer $CD4^+$ T cells and induce tolerance [15]. The suppressive activity of these cells may be a function of the cytokines they release. Recently, Kang *et al* examined IL-10 production by the $CDla^-DR^+$ inflammatory macrophages. At 72 h post irradiation, IL-10 mRNA expression was upregulated and the inflammatory macrophages secreted IL-10 into the culture medium. The authors postulate that these cells migrate to the draining lymph nodes, secrete IL-10, and activate immune suppression [16]. Of interest was the finding that although IL-10 mRNA was upregulated in UV-irradiated keratinocytes, no protein was secreted by these cells, which differs from the situation described after irradiation of murine keratinocytes [17] (see below).

One presumption from the above-mentioned studies, which mainly relied on *in vitro* techniques, is that UV-damaged LC, or UV-induced inflammatory macrophages, encounter antigen in the skin, migrate to the draining lymph node, and in the draining lymph node send a tolerance-inducing signal to the immune system. To determine whether this is indeed the case, Kripke and colleagues have employed an *in vivo* system in which mice are sensitized with fluorescein isothyocyanate (FITC) on the shaved ventral skin and $FITC^+$ APC are recovered from the draining lymph nodes 18 h later. The function of these cells is assessed by determining their ability to induce CHS in normal recipient mice. The APCs that induce CHS are dendritic in morphology, surface $I\text{-}A^+$, and radioresistant [18]. Moreover, some of these cells appear to be derived from epidermal LC, based on the presence of Birbeck granules in their cytoplasm [5]. These cells migrate to the lymph node from the skin, form clusters with reactive T cells, and stimulate CHS [19]. However, when the $FITC^+$ dendritic draining lymph node cells are isolated from mice sensitized through UV-irradiated skin and injected into normal recipient mice, CHS is depressed and hapten-specific suppressor T cells are activated [18]. Comparison of the ultrastructural and phenotypic properties of the draining lymph node cells from UV-irradiated or normal mice demonstrated several important differences. A significantly greater proportion of $FITC^+$ cells from the UV-irradiated mice expressed the macrophage markers, Mac-1, -2, and -3 and F4/80, and there were more $I\text{-}A^+$ cells in the draining lymph nodes of UV-irradiated animals. In addition, fewer dendritic lymph node cells isolated from UV-irradiated mice contained Birbeck granules. Kripke and colleagues suggest that the inability of draining lymph node cells to present antigen cannot be attributed to a reduction in MHC class II expression on the dendritic cells or to fewer numbers of antigen-bearing cells migrating to the lymph nodes. They suggest that the increased numbers of inflammatory cells in the lymph nodes is consistent with the data presented by Cooper and colleagues [14] and propose that different populations of antigen-bearing cells reach the lymph nodes following UV exposure, which may account for the induction of tolerance [20].

Effects of UVR on APC Populations in the Skin: Role of UV-Induced Epidermal Cytokines In addition to the direct effects of UVR on APC in the epidermis, UV exposure activates keratinocytes to secrete a wide variety of cytokines [21], many of which have been shown to modulate APC function. One such cytokine is tumor necrosis factor alpha (TNF-α). Extensive studies by Streilein and colleagues have pointed out an essential role for TNF-α in the induction of immune suppression following UVR [22]. Inbred strains of mice can be categorized according to the effects of UVR on CHS. UVB-susceptible (UVB-S) strains of mice are those mice in which CHS fails to develop following hapten sensitization through UV-irradiated skin, whereas in UVB-resistant mice (UVB-R), CHS develops normally when hapten is applied to the UV-irradiated skin. TNF-α appears to play a role in the UVB-S phenotype because injecting UVB-S mice with antibodies to TNF-α will convert them from non-responders to responders [23]. Genetic differences in the *Tnfa* locus have been proposed to regulate UVB resistance or susceptibility. Specifically, a unique mini-repeat in the 5′ regulatory region of the *Tnfa* gene of UVB-R mice has been suggested to interfere with transcription of the gene, thus conferring resistance. This micro-satellite is missing in UVB-S mice; hence, they produce TNF-α in response to UVR, and CHS is suppressed [24].

TNF-α affects epidermal LC function. Within 1–2 min of intracutaneous injection of TNF, LC withdraw their dendrites and become globular in appearance. These morphologic alterations appear to correlate with a transient delay in the ability of the treated LC to migrate to the regional lymph nodes [25]. Streilein and colleagues suggest that intracutaneous production of TNF alters the cytoskeleton of the LC, which modulates their migratory capacity, at least transiently, and prevents movement from the skin to the draining lymph node, thus interfering with the stimulation of T-cell immunity. It should be noted, however, that this interpretation is open to question because studies reported by Moodycliffe *et al* failed to confirm the inhibition of dendritic cell migration by UVR [26].

IL-10 is another cytokine produced by activated keratinocytes [17,27] that affects APC function [28]. IL-10, which is found as a 35–40-kDa homodimer in nature, is produced by T cells, B cells, mast cells, macrophages/monocytes, and keratinocytes. IL-10 was originally called cytokine synthesis inhibitory factor because of its ability to inhibit IFN-γ production by Th1 clones. IL-10 suppresses T-cell IFN-γ production by blocking the ability of APC to present the antigen to Th1 cells [28]. In addition, IL-10 has been shown to inhibit the production of a variety of other cytokines (IL-1β, TNF-α, granulocyte/macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor) by macrophages/monocytes [29] and interferes with the upregulation of the co-stimulatory molecule B7/BB1 on APC [30].

Although the exact molecular mechanism through which IL-10 blocks cytokine synthesis is not known, recent studies suggest that IL-10 treatment affects the stability of target mRNA. Kasama *et al* examined the affects of IL-10 on the secretion of IL-8 and macrophage inflammatory protein-alpha and -beta (MIP-α, MIP-β) by lipopolysaccharide (LPS)–treated neutrophils. They observed that the inhibition of chemokine secretion by IL-10 was associated with an accelerated decay in the half-life of IL-8, MIP-α, and MIP-β mRNA [31]. Furthermore, although IL-10 suppresses the release of IL-8, IL-1β, TNF-α, and MIP-α and β by LPS-activated neutrophils, the production of IL-1 receptor antagonist (IL-1ra) is increased after IL-10 treatment. Cassatellä *et al* report that increased synthesis of IL-1ra is associated with prolongation of the half-life of IL-1ra mRNA [32]. Thus, it appears that IL-10 alters cytokine synthesis by modulating mRNA stability.

A role for IL-10 in the inhibition of APC function following UV exposure has been suggested by Enk *et al* [33]. Whereas untreated and IL-10 pretreated LC presented antigen to Th2 clones, IL-10 pretreatment abolished the ability of LC to present to Th1 clones. The effect of IL-10 could not be attributed to a down-regulation of MHC class II antigen on the LC, but the introduction of untreated allogeneic LC restored the proliferation of the Th1 cells, suggesting that IL-10 is interfering with a co-stimulatory signal required for Th1 proliferation. Furthermore, IL-10–treated LC tolerize Th1 cells. This was discovered in experiments where T cells, cultured with IL-10–treated LC, were rescued and then restimulated with fresh LC and antigen. Whereas T cells isolated from control cultures responded to antigenic restimulation, those cells that were originally cultured with IL-10–treated LC did not respond to antigen. Because all the anergic T cells did proliferate when cultured with IL-2, the authors suggest that IL-10 pretreatment alters LC so that they induce clonal anergy in Th1 cells. In light of the fact that Rivas and Ullrich previously demonstrated that UV-irradiated keratinocytes secrete IL-10 [17], it is possible that the UV-induced inhibition of LC APC function *in vivo* may be due to the release of keratinocyte-derived IL-10.

UV-induced keratinocyte IL-10 can also have systemic effects. It has been known for quite some time that spleen cells from UV-irradiated mice were deficient in their ability to present antigen to T cells [34]. Although direct irradiation of APC by UVR efficiently inhibits APC function (see above), the limited ability of UVR to penetrate beyond the dermal-epidermal junction suggests that an indirect mechanism is involved in the *in vivo* impairment of splenic APC function. Because UV-irradiated keratinocytes release IL-10, we measured the ability of IL-10 to modulate splenic APC function in UV-irradiated mice [35]. Splenic adherent cells were isolated from normal mice, animals exposed to UVR, mice exposed to UVR and injected with monoclonal anti–IL-10, or mice exposed to UV and injected with control antibody. These cells were then used to present antigen to T-cell clones. Spleen cells from UV-irradiated mice were not able to efficiently present antigen to Th1 cells, and injecting the UV-irradiated mice with anti–IL-10 antibody completely restored the effect. Similarly, when splenic adherent cells were isolated from mice injected with recombinant IL-10, their ability to present antigen was significantly depressed. We also measured the effect that UVR had on antigen presentation to Th2 clones. Compared to the response observed when spleen cells were isolated from non-irradiated control mice, exposing mice to UVR resulted in an enhanced ability of their spleen cells to present antigen to Th2 cells. Moreover, injecting these mice with antibodies to IL-10 reversed this effect. Thus, these findings suggest that keratinocyte-derived IL-10 is involved in the systemic impairment of splenic APC function found in UV-irradiated mice. Furthermore, these observations suggest that one effect of keratinocyte-derived IL-10 is to systemically alter APC activity so that presentation to Th1 clones is suppressed, whereas presentation to Th2 clones is enhanced in UV-irradiated mice.

Previously, we demonstrated that the suppressor cells induced by UV exposure that regulate delayed-type hypersensitivity (DTH) are $CD3^+$, $CD4^+$, and $CD8^-$ [36,37]. Because keratinocyte-derived IL-10 promotes the activation of Th2 clones, we wished to determine whether the UV-induced $CD4^+$ suppressor cells are Th2-like cells that inhibit DTH by the release of cytokines, such as IL-4 and IL-10. To examine this question the following experiments were performed. Suppressor cells were induced in donor mice that were exposed to UVR and transferred into normal syngeneic recipient mice. These mice were then immunized with antigen and divided into four groups. One group received no further treatment, the second was injected with antibodies to IL-4, the third with antibodies to IL-10, and the fourth received control antiserum. As demonstrated previously, transferring suppressor cells from UV-irradiated mice into the recipients suppressed the induction of DTH. Injecting these mice with control antibody did not interfere with the transfer of suppression. When the recipient mice that received the UV-induced suppressor cells were injected with antibodies to IL-4 or IL-10, however, all suppressive activity was abrogated. When anti–IL-4 or anti-IL-10 was injected into recipient mice that were transferred with normal T cells, no adverse effect was noted, as the DTH response in these animals was comparable to that seen in the positive controls. From these findings we conclude that the suppressor cells induced following UV radiation mediate their immunosuppressive effect through the release of IL-10 and IL-4, supporting the hypothesis that the UV-induced suppressor cells are Th-2-like cells [38].

These observations may help clarify some of the "phenomenology" of systemic immune suppression that occurs after UV exposure. First, the target of UV radiation is the skin and, because most of the UV radiation is absorbed by the upper layers of skin, an indirect mechanism, such as the release of IL-10 by keratinocytes, is a likely explanation [17]. Second, a systemic impairment of APC function is associated with the systemic suppression of DTH [34,39]. Our recent findings suggested that this defect in APC function is caused by IL-10 [35], which presumably is released by UV-irradiated keratinocytes. Third, the phenotype of the suppressor cells ($CD3^+$, $CD4^+$, $CD8^-$) is consistent with the phenotype of Th2 cells. The antigen-specificity of the suppressor cells [40,41] can also be explained by this model. When the cells are transferred into recipient mice that are immunized with the same antigen as the donor, the transferred cells are activated, produce IL-4 and IL-10, and suppress the induction of DTH. But when the suppressor cells are transferred to recipient mice that are then immunized with a third-party antigen, the transferred cells are not activated, do not produce IL-4 and IL-10, and do not suppress. Studies are currently in progress to determine whether the UV-induced suppressor cells that control the development of tumors in UV-irradiated animals also mediate their immunosuppressive effects by the release of IL-4 and IL-10.

Urocanic acid, a deamination product of histidine, is abundant in the upper layers of the epidermis. Upon exposure to UVR, urocanic acid is isomerized from the trans- to the cis-isomer. It has been suggested by De Fabo and Noonan [42] that urocanic acid is the photoreceptor in the epidermis, and data from a number of laboratories have documented an immunosuppressive role for cis-urocanic acid [43]. Cis-urocanic acid also appears to mediate its immunosuppressive effects by altering APC function [44]. Noonan *et al* isolated splenic dendritic cells from normal mice, mice exposed to UVR, or mice injected intravenously with cis- or trans-urocanic acid. These cells were then used to present antigen to primed T cells. Injecting mice with 100–200 μg of cis-, but not trans-, urocanic acid significantly depressed the APC function of splenic dendritic cells. For the most part, the magnitude of the suppression observed following administration of cis-urocanic acid was similar to that seen following UV exposure. Modulation of cell-surface markers (FcR and MHC class II) or production of suppressive factors by the splenic dendritic cells could not explain the decreased ability of the splenic cells from cis-urocanic acid–injected mice to present antigen.

Cis-urocanic acid also suppresses epidermal LC APC function. Kurimoto and Streilein [45] observed that intraepidermal injections of cis-urocanic acid mimicked the effects of UVR and prevented

the induction of CHS when the hapten was applied to the treated skin. In addition, intradermal injection of cis-urocanic acid decreased the density of epidermal LC and altered their morphology. It is of interest to note that injecting anti–TNF-α antibodies restored the number of I-A$^+$ LC in cis-urocanic acid–treated skin. Kurimoto and Streilein suggest that cis-urocanic acid is binding to receptors on epidermal keratinocytes and inducing the release of TNF-α, which is then affecting LC function and morphology. Therefore, these findings suggest that cis-urocanic acid, like IL-10, interferes with APC function locally at the site of irradiation and induces a systemic defect in APC function in the UV-irradiated host.

Modulation of Co-Stimulatory Molecules by UVR As mentioned above, co-stimulatory molecules on the surface of APC play an important role in T-cell activation. Transfecting cells with the genes encoding co-stimulatory molecules, such as intracellular adhesion molecule-1 (ICAM-1) [46] or B7 [47], together with MHC class II antigens, will promote antigen presentation and/or accessory cell function. Alternatively, treating APC with antibodies against ICAM-1 will interfere with antigen, mitogen, and anti-CD3–induced MHC-restricted T-cell proliferation [48,49]. Within the epidermis keratinocytes and LC are known to express (either constitutively or following induction) ICAM-1. Moreover, UVR is known to modulate the expression of ICAM-1 and hence may affect APC function by altering their ability to express co-stimulatory molecules [50].

To date, although the expression of ICAM-1 on epidermal keratinocytes has been studied in some detail, less is known about B7 and ICAM-1 expression on LC. Keratinocytes in normal skin or long-term cultured keratinocytes do not express ICAM-1 on their surface. ICAM-1 expression is up-regulated *in situ* during inflammatory skin disease or after treating keratinocyte cultures with cytokines (IFN-γ, TNF-α, and TNF-β) [51,52]. Combinations of IFN-γ plus TNF-α or IFN-γ and TNF-β act in a synergistic fashion to induce ICAM-1 expression on keratinocytes. The most likely source of TNF-α *in vivo* are the keratinocytes themselves and, in all probability, the TNF-β and IFN-γ is produced by infiltrating T cells, which by inducing keratinocytes to express ICAM-1 provides a target for T-cell LFA-1, thus facilitating and maintaining the T-cell infiltrate.

How does UV light affect ICAM-1 expression? Exposing keratinocytes to UVR inhibits the up-regulation of ICAM-1 expression [51,52]. This occurs in a dose-dependent manner and occurs with sublethal doses of UVR. The effect of UVR on ICAM-1 expression is biphasic. Suppression of cytokine-induced up-regulation of ICAM-1 expression was noted 12 h after UVR, but by 48 h expression of ICAM-1 by keratinocytes was greatly enhanced [51,52]. This effect may be related to the production of cytokines by the UV-irradiated keratinocytes themselves, because supernatants from these cells, collected 48 h after irradiation, up-regulated ICAM-1 expression when added to non-irradiated keratinocytes [53]. Of interest was the observation that treating the supernatants with anti–TNF-α antibodies did not abrogate this effect, whereas treating the supernatants with anti–IL-1α did [50].

ICAM-1 is also expressed on LC, and antibodies to ICAM-1 can interfere with the accessory function of LC. Moreover, UVB exposure blocks the up-regulation of ICAM-1 normally found during *in vitro* culture of LC [54]. Whether down-regulation of ICAM-1 expression *in vivo* contributes the UVR-induced immune suppression is not clear. And although it appears that B7 is expressed on cultured human LC [55], and IL-10 has been shown to down-regulate the expression of B7 on human monocytes [56], it is not known whether UVR alters the expression of these co-stimulatory molecules on LC.

Effect of UVR and Epidermal Cytokines on the Induction of Tumor Immunity Most of the studies summarized above (including our own) have taken the "reductionist approach" to studying the role of UVR in immunity. Break the system down to its simplest parts, and study the effect of a limited number of variables on one aspect of immunity. For example, in our studies, we have examined the effect that injecting monoclonal anti–IL-10 has on the UV-induced suppression of DTH, CHS, or systemic APC function. However, it is clear that the immune system is a dynamic, self-regulating system, with a variety of redundant control mechanisms built in. So, although a reductionist approach is at times desirable, and often the only way to dissect complicated immunologic pathways, we all must remember that we are at times only taking a "snapshot" and not looking at the complete picture. One experimental model system that illustrates the dynamic nature of the interplay between UV radiation and cytokines on epidermal APC function has been described by Granstein and his colleagues [57]. In these experiments, I-A$^+$ epidermal APC, presumably LC, are pulsed with tumor antigen (S1509a cells) and then used to immunize mice. The mice are then challenged with viable tumor cells, and tumor incidence is measured. It was observed that repeated immunization of naive mice with tumor-pulsed, I-A$^+$ epidermal cells generated protective immunity. The response was tumor specific, required immunization with live I-A$^+$ cells, and was MHC restricted. The capacity of the epidermal I-A$^+$ cells to present antigen is modulated by a variety of cytokines and environmental factors. Pre-incubation of the I-A$^+$ epidermal cells with GM-CSF, a factor which is known to promote the maturation of LC into potent immunostimulatory cells [58], was required for the induction of tumor immunity. When GM-CSF treated epidermal cells were exposed to UVR prior to antigen pulsing, a UV-dose–dependent inhibition of tumor immunity was noted. UV exposure after antigen pulsing also affected the ability of the epidermal cells to present antigen. The effect of treating the epidermal APC with TNF-α was also measured. Co-culturing the APCs with GM-CSF and TNF-α did not adversely affect the induction of tumor immunity. Likewise, incubating the APC with TNF-α prior to incubation with GM-CSF did not adversely affect APC function. Incubating the epidermal cells with 100 U/ml of TNF-α after GM-CSF treatment, on the other hand, did completely abolish the induction of tumor immunity. Thus, the timing of TNF-α treatment in regard to GM-CSF exposure is a critical factor in whether efficient antigen presentation occurs. Treatment before or at the time of GM-CSF administration does not interfere with the maturation signal delivered to the LC but, if TNF-α follows GM-CSF, the immunostimulatory activity of the LC is abolished [59]. The opposite result is seen when IL-10 is used. Treating the epidermal cells with rIL-10 (20 ng/ml) prior to or during GM-CSF exposure abolished all APC activity. However, IL-10 treatment after GM-CSF exposure did not have any adverse affect on the APC function [60]. Similarly, treating the epidermal cells with IFN-γ during GM-CSF exposure inhibited the APC function of the I-A$^+$ epidermal cells [61]. These results confirm the inhibitory effects of UVR and epidermal-derived cytokines on APC function. Perhaps more importantly, however, they point out the dynamic nature of the interaction between UVR, UV-induced cytokines, and APC.

What Is the Photoreceptor in the Skin for UV-Induced Immune Suppression? To date, two molecules have been suggested as the photoreceptor in the skin that initiates the immune suppression caused by UVR. Based on observations that placed the location of the photoreceptor in the stratum corneum, and findings that demonstrated that the action spectrum for photoimmunosuppression closely matched the action spectrum for the isomerization of urocanic acid, De Fabo and Noonan suggested that the photoreceptor for UVR in the skin is trans-urocanic acid. After irradiation with UVB, trans-urocanic acid isomerizes to cis-urocanic acid, which then activates the immunosuppressive pathway [42]. Over the years, data from a number of laboratories have supported this hypothesis by demonstrating the immunosuppressive properties of cis-urocanic acid (see above and [43]). Recently, however, data has been presented that suggests that the *in vivo* action spectrum for photoisomerization of urocanic acid differs significantly from the action spectrum for immune suppression [62]. In addition, Moodycliffe *et al* report that although the broad-band UVB (270–350 nm)

from a fluorescent sun lamp did suppress the induction of CHS, narrow-band UVB (311–312 nm) did not, regardless of the fact that both light sources caused the photoisomerization of urocanic acid [26]. Thus, there is some question as to whether urocanic acid is the only photoreceptor in the skin. Studies by Kripke and colleagues have suggested that DNA may also serve as the photoreceptor. Two experimental approaches were used in these studies. Applegate *et al* observed that irradiating the marsupial *Monodelphis domestica* with photoreactivating light after UV exposure reversed the UV-induced suppression of CHS [63]. Because irradiating *M. domestica* with visible light activates the photoreactivating enzyme that repairs pyrimidine dimers [64], these studies suggest that DNA is the photoreceptor. The second approach employed the strategy of using liposomes to introduce the bacteriophage excision repair enzyme, T4 endonuclease V, into mice [64]. Animals were exposed with UVR, and then the liposomes suspended in a Hydrogel vehicle were painted onto the skins of the mice. Both the UV-induced suppression of CHS and DTH was inhibited when the enzyme-containing liposomes were applied to the skins of the irradiated animals. No inhibition of suppression was observed when control liposomes containing a heat-inactivated preparation of enzyme were applied to the skin. Moreover, the induction of UV-induced suppressor T cells was inhibited when the liposomes containing the endonuclease repair enzyme were applied to the skin [65]. These findings confirm the data obtained with the marsupials and suggest that DNA is the photoreceptor for UV-induced immune suppression. It is of interest to note that activating the photoreactivating enzyme *in situ* or using liposomes to introduce the excision repair enzyme also interferes with the induction of skin cancer by UVR [65,66].

SUMMARY, CONCLUSIONS AND QUESTIONS FOR THE FUTURE

It is clear that UVR is an immunosuppressive agent and its ability to down-regulate immunity has been linked to its carcinogenic potential [67,68]. A key effect of UVR on the immune system is the modulation of APC function. UVR alters APC function directly by affecting epidermal LC [7,8] or indirectly by inducing keratinocytes to release immunomodulatory cytokines [33,45]. These cytokines appear to work both locally and systemically to alter APC function [35,44].

Why have redundant mechanisms evolved to suppress the immune response after UV exposure? Some have suggested that the mutagenic potential of UVR coupled with the need to maintain skin homeostasis resulted in the development of these redundant suppressive mechanisms. One consequence of UVR exposure may be the development of new or altered skin antigens that the immune system recognizes as foreign. The pressure to prevent an autoimmune reaction to UV-modified skin antigens may be the driving force behind the evolution of UV-triggered immune suppression [1].

A common theme found in a number of the studies reviewed here is the UV-induced activation of Th2 cells coupled with the induction of Th1 cell tolerance [9,33,35]. Because Th1 cells generally help cell-mediated immune reactions, such as DTH, CHS, and tumor rejection, the suppression of this arm of the immune system fits in with the well-described selective suppression of immunity after UV exposure [1]. Does this shift from a Th1-like response to a Th2-like immune reaction also reflect the pressure to avoid anti-skin auto immune reactions, or are other mechanisms involved?

What other immune reactions are regulated by UVR? Animal studies from a number of laboratories have clearly shown that UV exposure can interfere with the response to and clearance of some infectious organisms [69,70]. Does the UVR found in sunlight play any role in susceptibility of humans to infectious agents? And although it is acknowledged that ozone depletion will contribute to an increased incidence of human skin cancer, will depletion of the ozone layer have any affect on human susceptibility to infectious agents?

Table I. Important Questions for Future Research

- What is the UV photoreceptor—urocanic acid or DNA?
- Which UV-induced epidermal "cytokine" is essential for the induction of immune suppression, IL-10, TNF-α, IL-1, cis-urocanic acid, PGE_2, or others, as yet undiscovered? Do they work in concert or alone to induce immune suppression?
- Which cell produces UV-induced suppressive cytokines, the keratinocyte or the infiltrating macrophage?
- Does UV-induced immune suppression play a role in the susceptibility of humans to infectious agents?
- How can we effectively limit sun exposure? Are the current generation of sunscreens effective at protecting against the immune suppressive effects of UV radiation?

How can we prevent the deleterious immunosuppressive effects of UVR? Total avoidance is impractical, and efforts of late have been designed to limit sun exposure. Chemical sunscreens are an important part of this strategy. Although sunscreens are quite effective at preventing sunburn and erythema and are thought to protect against the induction of skin cancer by preventing DNA damage, it is not clear that they prevent the immunologic damage caused by UVR. In studies by Kripke and colleagues, sunscreens were very effective at protecting against the inflammation caused by UVR, but only marginally effective at preventing UV-induced immune suppression [71,72]. Of course, these results must be viewed with caution because FS-40 sunlamps, which emit shorter wavelengths of UV radiation than solar radiation were employed; therefore, extrapolating these results to humans is difficult. These findings do indicate the need for more research into the prevention of UV-induced immunologic damage by chemical sunscreens.

Finally, some efforts have been made at ameliorating the immune suppressive effects of UVR. Strickland and colleagues found that topical application of a gel extract from *Aloe barbadensis* to murine skin after UV exposure can block the induction of immune suppression [73]. Similarly, studies from my laboratory have indicated that treating mice systemically with IL-12, which prevents the differentiation of Th2 cells [12], after UV exposure blocks the induction of immune suppression [74]. Hopefully, in the future it may be possible to prevent the induction of immune suppression in people who spend a little too much time in the noon-day sun.

This work was supported by grant AR 40824 from the National Institutes of Arthritis and Musculoskeletal and Skin Disease.

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